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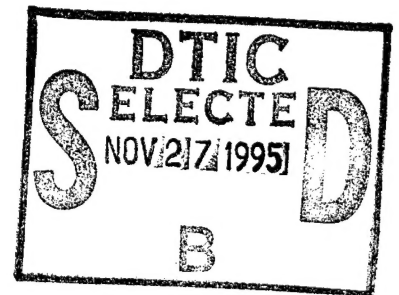
TITLE: Utilization of an NCI Infrastructure to Evaluate Breast Cancer Patient Outcomes of Importance in Determining Priorities for New Health Care Reform

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This project develops a novel clinical curriculum that utilizes resources from diverse disciplines. I have combined sub-specialty training in medical oncology with formal courses in biostatistics, epidemiology, and health policy research, in order to develop expertise in clinical trials methodology and health care reform. Preliminary training involved breast cancer specialization in a multi-disciplinary clinic, and completion of a Clinical Research Scholars Program in order to develop a foundation in outcomes research. The second phase of the project involves the development of specific models and instruments to analyze breast cancer treatment options. Such tools will be invaluable in an analysis of the quality of medical care received by women with breast cancer. Moreover, they are important measurements of the impact that existing physician practice has on the quality and cost of health care. Outcomes research methodology will be applied to a comprehensive review of bone marrow transplantation for breast cancer, and subsequently will be utilized in the implementation of an outpatient high-dose chemotherapy program with particular emphasis on managed care practices and cost-benefit analysis. The goal is not only to learn how to properly conduct research, but ultimately to incorporate outcomes assessment into the structure of clinical trial design.

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FOREWORD

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INTRODUCTION

Background

Last year 182, 000 women in the United States were diagnosed with breast cancer. Experts agree that median survival has not changed appreciably in the past 5 decades, and it is estimated that over 45,000 women will die each year from metastatic disease. Because so many women are affected, breast cancer research receives the largest allocation of federal funding in this country. In 1993, over 260 million federal research dollars will be invested in breast cancer research. Furthermore, this funding does not include the enormous resources spent each year by Third-party insurers for the screening, diagnosis and treatment of women with breast cancer in the United States.

Bone marrow transplantation technology has advanced dramatically over the past decade. Enthusiasm for this method of treatment has flourished, despite the absence of any prospective randomized data to compare this investigational treatment with conventional chemotherapy for advanced disease. A variety of studies clearly document higher complete response rates and overall response rates in patients treated with bone marrow transplant, these patients have similar survival duration, and the duration of response is no different when compared to patients treated with conventional therapy. Unfortunately public expectation of this treatment far exceeds the reality of published results.

Moreover, bone marrow transplantation has generated an intense health policy debate, because the financial cost of such treatment is enormous. Furthermore, because third-party insurers still consider this treatment investigational, they won't pay the over \$100,000 estimated cost for each transplant. As a result, patients are now suing insurance carriers who don't cover this therapy. Thus, the lack of controlled clinical trials has resulted in data which are extremely difficult to interpret and public expectations which are currently unfounded.

As a consequence of uncontrolled trials, data exists that allows an investigator to support a variety of conclusions. This dilemma is highlighted by two large literature reviews that appeared almost simultaneously in 1992 oncology journals, but came to opposite conclusions. K. Antman, a pioneer in the development of high-dose chemotherapy regimens used with autologous bone marrow transplant, reviewed all trials in which women with advanced breast cancer who were treated with bone marrow transplantation. In this article,

"Progress in Chemotherapy for Metastatic Breast Cancer" (*Seminars in Oncology* 19: 317-332, 1992), three sets of uncontrolled studies were viewed favorably based on a comparison of complete response rates to historical controls. The authors conclude that, "un-maintained responses appear to be encouraging in patients who are transplanted early in the course of their disease, and after a good response to standard dose chemotherapy."

David Eddy of the Center for Health Policy Research and Education at Duke University, and advisor to the Blue Cross / Blue Shield National Association Technology Assessment Panel reaches an entirely different conclusions from the same clinical trials data. His review, "High-Dose Chemotherapy with Autologous Bone Marrow Transplantation for the Treatment of Metastatic Breast Cancer" (*Journal of Clinical Oncology* 10: 657-670, 1992), explains that "firm conclusions are not possible because of the lack of controlled studies, and the presence of numerous biases.

I. Craig Henderson also asserts that current breast cancer trials in women with advanced disease are "sufficiently promising to justify comparative trials, but insufficient to conclude that the therapy is superior to more conventional treatments." In his editorial, "Window of Opportunity," he further outlines the scope of the debate involving the high costs of bone marrow transplant in terms of toxicity and the shrinking resources available to fund large clinical trials. (*Journal of the National Cancer Institute* 83: 894-896, 1991) Henderson reports that the National Blue Cross / Blue Shield Association recently created a fund to help the National Cancer Institute sponsor clinical trials. Such collaboration between third-party payers and clinical investigators is imperative in the current setting of health care reform, in order to cover the "costs of legitimate research approved by peer review groups outside the investigator's own institution."

The controversy surrounding high-dose chemotherapy as a treatment for breast cancer has recently intensified with the first publication of a randomized trial supporting concept of dose-intensity. (*Journal of Clinical Oncology* 13(10):2483-2489, 1995) High dose chemotherapy (HD-CNV) was administered as a two step tandem regimen at doses of 2.4 g/m² cyclophosphamide, 35-45 mg/m² of mitoxantrone, and 2.5 g/m² of etoposide. The control arm used 6-8 cycles of a conventional dose schedule (CNVr) with 600 mg/m² of cyclophosphamide, 12 mg/m² of mitoxantrone, and 1.4 mg/m² of vincristine. The response rates were significantly higher in the high-dose patients (95% vs 53%) with 51% of the high-dose patients achieving a complete response. Disease-free survival was prolonged with HD-CNV (80 weeks vs. 34 weeks) and overall survival was twice that of the standard dose

regimen (90 weeks vs. 45 weeks). The statistical significance of these survival differences was not reported.

Although not definitive, this positive study will be championed by advocates of dose intensity, and health policy decisions regarding patients selection, specific drug regimen, and insurance reimbursement now have an urgent priority.

Proposal Outline

This proposal creates a novel curriculum in clinical outcomes research that utilizes multiple resources from diverse disciplines.

A.G. Mulley, a pioneer in the field of outcomes research, stresses the increasing problems associated with cost and access to health care. In a draft manuscript, "Outcomes Research: Potential, Prospects & Policy Implications," he defines outcomes research as the "generation, collection, and analysis of information about the results or outcomes of medical care for the purpose of learning how to improve those results. He outlines 4 specific types of research that directly applies to the debate about bone marrow transplantation in advanced breast cancer:(Outcomes Research: Potential, Prospects and Policy Implications. 1993)

- 1) Studies that observe variation in the process of medical care.
- 2) Studies that observe variations in the outcomes of care.
- 3) The development of instruments to measure outcomes of care.
- 4) The study of patient preferences.

Eddy also addresses the issues of patient outcomes in his review, when he describes the 5%-15% treatment related mortality involved in bone marrow transplantation, as well as the complication rate of 30%. He also defines outcomes that have not yet been specifically analyzed in current clinical trials, to the detriment of drawing legitimate conclusions.

- 1) Overall survival
- 2) Relief of symptoms
- 3) Risk of treatment
- 4) Side effects of treatment

Eddy finally concludes that response rates are not outcomes, and thus, can not be sole basis for treatment decisions. Instead researchers must define how patient outcomes can and should affect medical decision making. Outcomes research methodology will provide useful tools for the analysis of the transplant controversy. Specific questions to be addressed remain, which have critical importance in resource allocation and health care reform:

- 1) Do women live longer with a bone marrow transplant
- 2) Do women spend a significantly greater period of time without side effects of therapy or symptoms of disease than they would with conventional therapy?
- 3) What do women understand are the benefits of transplant?
- 4) What are physician expectations for this therapy?
- 5) Do the benefits of treatment justify the costs?

Thus, high-dose chemotherapy with autologous bone marrow transplant represents an enormous public health issue, and this clinical fellowship proposal has been developed to prepare a clinical oncologist for the academic arena of health services research and health care reform. Sub-specialty training in medical oncology will be combined with formal courses in biostatistics, health services research and technology assessment, in order to develop expertise in clinical trials methodology and health policy issues.

Preliminary work based on this training will involve the development of specific outcome models and instruments to assess individual patient preferences and satisfaction with various treatment options. Such tools will be invaluable in an analysis of the quality of medical care received by women with breast cancer in the United States. Moreover, they are important measurements of the impact that existing physician practice has on the quality and cost of health care.

A formal internship has been arranged with the Medical Advisory Panel of the National Association of Blue Cross Blue Shield. This background will then serve as the foundation for the design of an outpatient transplant protocol the can serve as a model for comparison and cost-effectiveness analysis, and develop a career in medical oncology and outcomes research.

BODY OF REPORT

During the past 12 months, I successfully completed both objectives for the first year of the project.

1) Develop an in-depth understanding of the natural history and medical management of breast cancer.

The essential core of this curriculum involved in-depth specialty training in the treatment of breast cancer patients. I have completed the second year of a clinical fellowship in medical oncology at the University of California, San Francisco, and focused on the outpatient care of women with breast cancer at the UCSF / Mount Zion Breast Cancer Clinic will focus on the outpatient care of women with breast cancer. This multi-disciplinary clinic provides a unique opportunity to focus on a select group of patients under the guidance of Drs. I. Craig Henderson, Chris Benz, Charles Dohlbaum and Debu Tripathy from the division of Medical Oncology, Drs. Laura Esserman and William Goodson from the Department of Surgery, and Dr. Laurence Margolis from the department of Radiation Oncology. Drs. Henderson, Tripathy, Esserman and Margolis have primary offices in the Breast Clinic, and will provide daily instruction. All of these physicians are breast cancer specialists, who serve as primary faculty mentors during weekly clinics and conferences. I will continue to participate in this weekly clinic and multi-disciplinary conference for the remainder of my fellowship training project.

As a result of my participation in the breast cancer multi-disciplinary clinic, I have developed two Phase II/III clinical trials involving Vinorelbine as a treatment for metastatic breast cancer. These studies will incorporate significant quality-of-life and resource utilization outcomes that are a direct result of this project. Both trials have just been accepted by the Human Subjects Committee, and are open for patient accrual.

2) Master the methodology of clinical trial design

During the first year of this research fellowship, I completed the Clinical Research Scholars Program at U.C.S.F. This combined program in the departments of Medicine, Epidemiology, and Biostatistics consisted of a 1-year core curriculum in clinical research, with a specific goal to "train the scholar to conceive, plan, and conduct state of the art clinical research, and analyze the results of research appropriately." The Clinical Scholars Program included comprehensive training in statistical methods and data analysis, as well as the specifics of clinical trial design. Particularly relevant topics included decision analysis, cost-effectiveness research, and computer-based data management. During the monthly "Work in Progress Seminar," I designed a Phase II trial involving Vinorelbine and Paclitaxel as a combination treatment for metastatic breast cancer. This trial has been approved by the Human Subjects Committee, and will be open to patient accrual in September.

The second half of the course involved in-depth health care policy and outcomes research, and was taught by faculty from the Department of Epidemiology and the Institute for Health Policy Studies. These 3 hour/week didactic sessions have provided an excellent foundation for future study, particularly cost-benefit analysis and health care reform. During this phase of my training, I published a comprehensive review of high-dose chemotherapy with autologous bone marrow transplant for women with breast cancer, and emphasized the health policy debate surrounding this controversial treatment (Smith, GA, Henderson, IC, "High-dose Chemotherapy with Autologous Bone Marrow Transplantation for the Treatment of Breast Cancer: The Jury Is Still Out," *Important Advances in Oncology 1995*, DeVita, V.T. ed, 1995, pp. 201-214.)

Based on the foundation provided by the breast clinic and the Clinical Scholars Program, I have two key objectives for the second year of the project:

- 3) **Learn the fundamentals of patient outcomes research, medical economics, and health care policy, in order to study the role of patient outcomes in the development of new technology.**

This fellowship proposal involves patient outcomes research training, and the application of specific tools to maximize patient outcomes in the development of new technology.

A) Institute for Health Policy Studies

During the second year of this proposal, I will enroll at the Institute for Health Policy Studies at the University of California, San Francisco, founded by Dr. Phil Lee. Dr. Hal Luft, Acting Director of the Institute, has offered his support for a project that involves health services research and health policy training at the I.H.P.S. Under the guidance of Dr. Luft, I will attend specific postgraduate seminars which emphasize current health policy themes, including the "The Art and Science of Health Services Research," and "Translating Research Into Policy." The I.H.P.S. also supports individual research projects and provides each fellow with a mentor and preceptor.

My major emphasis will be the study of patient preferences, physician decision-making, quality of life issues associated with high-dose chemotherapy and peripheral blood stem cell support as a treatment for breast cancer. Specifically, I will utilize cost-effectiveness and decision analysis methodology to create a detailed algorithm in order to identify the optimal treatment for specific groups of women with advanced breast cancer and patients who would be appropriate candidates for high-dose adjuvant therapy. I expect this model to appear in peer-reviewed literature, and to serve as a tool for managed care and insurance company reimbursement decisions.

B) Blue Cross/Blue Shield Internship

The health policy experience gained at the I.H.P.S. will allow me to work with the Blue Cross/ Blue Shield Association, in order to learn the principles of technology assessment. Naomi Aronson, PhD., Director of Technology Evaluation at the Blue

Cross and Blue Shield National Association, has invited me to develop an internship working with the Medical Advisory Panel. I will either work directly with this panel, or develop a project with the Northern California Division in the development of specific guidelines for the approval and implementation of high-dose chemotherapy as a treatment for breast cancer.

C) Stanford Business School health policy work

In preparation for this project in technology assessment, I will audit an advanced Health Policy course at the Stanford Business School. I have contacted Dr. Alain Enthoven, a pioneer in the field of Health Care Economics, and during the second year of this fellowship, I will take both "Political Economy of Health Care," and "Cost-Benefit Analysis in Health Care."

D) Managed care contract negotiations

Finally, I hope to incorporate this field experience with technology assessment projects at other large third-party organizations, such as Health Net or Kaiser Permanente in San Francisco, in order to obtain an accurate assessment of the financial and human resources required to conduct clinical trials. The crucial issue remains: "who will fund the ever increasing costs of these clinical trials?" I am especially concerned about the importance of these issues in the development of the new national health care plan.

4) Apply outcomes research models to specific projects for high dose chemotherapy as a treatment for breast cancer.

A) UCSF Pilot outpatient ABMT program

The ultimate goal of my proposal will be to apply this diverse training background to develop specific outcomes research tools and then to apply these instruments to specific breast cancer research projects. I no longer plan to utilize the Cancer and Leukemia Group B as the major resource for this phase of the project. However, due to persistently slow accrual to randomized cooperative group trials, the data will likely not be available for analysis during the timetable

outlined in this project, and both internships with CALGB have been postponed indefinitely.

Instead, I have broadened the scope of my specific outcomes projects to include a specific project at the University of California, San Francisco. Dr. Lee Goldman, Chairman of the Department of Medicine has agreed to serve as a mentor for this breast cancer project related to health care outcomes of particular importance in a Managed Care environment.

I will develop an outpatient-based high-dose therapy protocol which will emphasize cost-effectiveness results from previous work. The entire treatment plan will prioritize patients outcomes, and will be structured in such a fashion that additional research can be readily obtained.

Critical questions at this phase of the project include :

- 1) What outcomes are feasible to measure?
- 2) Can these outcomes be accurately and reliably measured?
- 3) Are the measurable outcomes important to patients?
- 4) Which outcomes are most important to a managed care plan?
- 5) What resources are required for HDC/ABMT?
- 6) Can a cost-benefit analysis identify a superior treatment?

An outpatient program of high-dose chemotherapy with bone marrow transplantation provides an excellent model for the study of patient outcomes research. Until recently, the lack of controlled clinical trials generated intense debate within the medical profession about the effectiveness of this treatment, and a tremendous enthusiasm in the community for an unproven treatment. Now that randomized trials are providing supportive evidence in certain patients, the need for proper outcomes-based protocol design is imperative, particularly in the Managed Care driven market of Northern California.

B) Computer- based decision analysis

I am no longer planning a Shared Decision Making Program, as other investigators have already developed existing software for this purpose.

Instead I have joined a steering committee at the University of California to develop a computer-based order entry system for the entire hospital. I feel that this technology will allow for cost-effectiveness and toxicity outcomes analysis that will provide a foundation for future projects in oncology. Specific priorities include chemotherapy toxicity, physician prescribing patterns, and resource utilization involved in the treatment of women with breast cancer .

CONCLUSIONS

This annual report documents the successful completion of the 1st year of a novel clinical curriculum in outcomes research training. I have completed sub-specialty training in breast cancer through participation in a unique, multi-disciplinary clinic at the University of California, San Francisco. This training has resulted in several independent Phase II/III trials of new treatments for breast cancer, which emphasize importance of quality of life and resource utilization outcomes as primary reassert endpoints. I have also completed the Clinical Research Scholars Program, which has provided an excellent foundation for health care outcomes research.

I am now embarking on the second phase of the project, which involves specific research in cost-benefit analysis at the Institute for Health Policy Studies. High-dose chemotherapy with bone marrow transplant will provide the model for a detailed decision-analysis project. I have also initiated plans to develop a managed care analysis of HDC/ABMT, and will assist in the development of an outpatient protocol at our institution, which will serve as a model for subsequent outcomes analysis. During the final year of the project I will embark on a scheduled internship at the Blue Cross/Blue Shield Technology Assessment Panel in order to incorporate outcomes research methodology into health care policy formation. Finally, computer-based order entry system will serve as a template for outcomes research projects involving breast cancer treatment at the University of California, San Francisco.